Inorganic Chemistry Communications 157 (2023) 111396

Contents lists available at ScienceDirect

Inorganic Chemistry Communications

journal homepage: www.elsevier.com/locate/inoche

Short communication

Antimicrobial activities of bis-(*N*-alkylbenzimidazole)-cobalt(II) and zinc (II) complexes

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ARTICLE INFO

Keywords:
Benzimidazole ligand
Cobalt
Zinc
X-ray crystallography
Antimicrobial activity
Antifungal activity

ABSTRACT

Eight benzimidazole precursors (**L**), namely 1-allyl-benzimidazole, 1-methallyl-benzimidazole, 1-isopropyl-benzimidazole, 1-(3-methyloxetan-3-yl)methyl-benzimidazole, 1-allyl-5,6-dimethyl-benzimidazole, 1-methallyl-5,6-dimethyl-benzimidazole, 1-isopropyl-5,6-dimethyl-benzimidazole and 1-(3-methyloxetan-3-yl)methyl-5,6-dimethyl-benzimidazole, were coordinated to cobalt(II) and zinc(II) cations to form complexes of the type $[MCl_2\mathbf{L}_2]$. Single-crystal X-ray structures were determined for two cobalt(II) and for one zinc(II) complexes and confirmed their tetrahedral molecular geometry. The antibacterial and antifungal activities of these two series of cobalt(II) and zinc(II) complexes were studied against Gram-negative (*Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii* and *Klebsiella pneumoniae*), Gram-positive (*Staphylococcus aureus, methicillin-resistant S. aureus* and *Enterococcus faecalis*) bacteria and fungal strains (*Candida albicans* and C*andida glabrata*). Overall, cobalt(II) complexes were more effective than the zinc(II) complexes against all microorganisms. The most significant results were obtained with the two dichloro-*bis*(1-allyl-5,6-dimethylbenzimidazole)-cobalt(II) and dichloro-*bis*(1-methallyl-5,6-dimethylbenzimidazole)-cobalt(II) complexes against *Candida albicans* and *Candida glabrata* fungi with measured minimal inhibitory concentrations as low as 0.024 μmol/mL, values close to those obtained with the commercially available drug Flucanozole (0.020 μmol/mL).

1. Introduction

Bacteria are the leading cause of common infectious diseases.[1] Indeed, they can produce enough toxins to harm the human body, which can lead to serious and sometimes fatal complications, such as kidney failure and toxic shock syndrome.[2,3] Although many antibiotic drugs have been used, epidemics and antibiotic resistance still search for new and more effective antibacterial drugs necessary.[4–16].

In this context, azoles, which are an important class of *N*-donor heterocyclic compounds and due to their antibacterial and antifungal activities, play an important role in the pharmaceutical industry.[17–19] Thereby, the benzimidazole moiety is found in several commercially available drugs such as anthelmintic (albendazole, mebendazole, triclabendazole), fungicides (benomyl), and proton pump inhibitors (omeprazole, lansoprazole, pantoprazole) (Fig. 1).[20–22].

Furthermore, the benzimidazole ring can easily be coordinated, via their nitrogen atom, to transition metals, which releases the anticancer, antihypertensive, antihistamine or antibacterial properties of these aromatic compounds.[23–27] The use of organometallic complexes as antimicrobials is motivated by the fact that they have a distinct mode of action than organic antibiotics and can therefore be applied in the treatment of recalcitrant microbial infections. In particular, zinc and cobalt complexes, two natural elements present in human body,[28,29] have recently been studied. For example, the group of Li has demonstrated that bis zinc(II) complex **A** (Fig. 2) displayed good and broad spectrum antimicrobial activities with minimal inhibitory

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https://doi.org/10.1016/j.inoche.2023.111396
Received 26 June 2023; Received in revised form 4 September 2023; Accepted 7 September 2023
Available online 9 September 2023

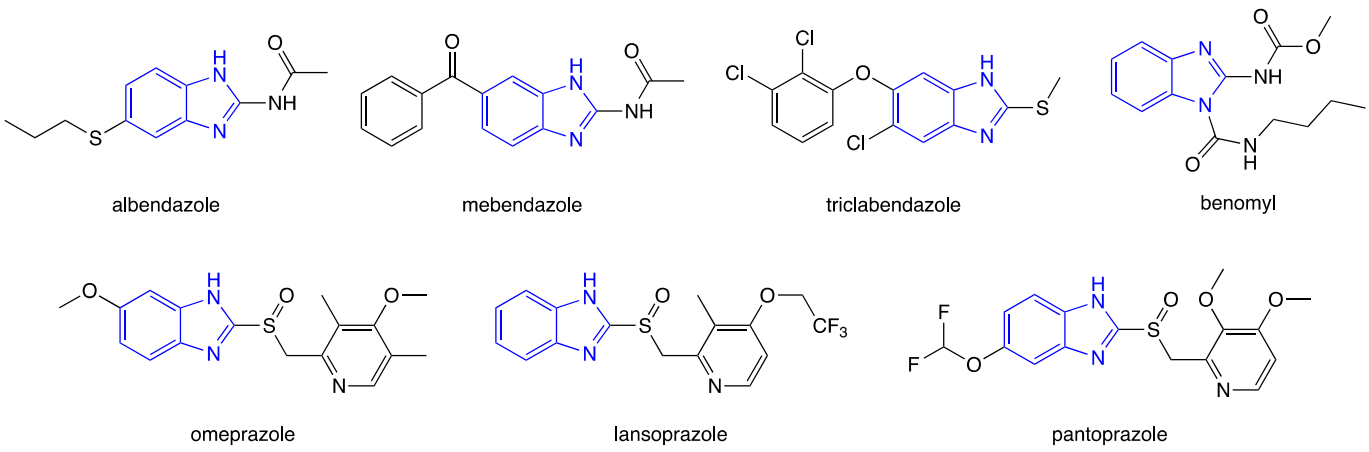


Fig. 1. Drugs based on benzimidazole skeleton.

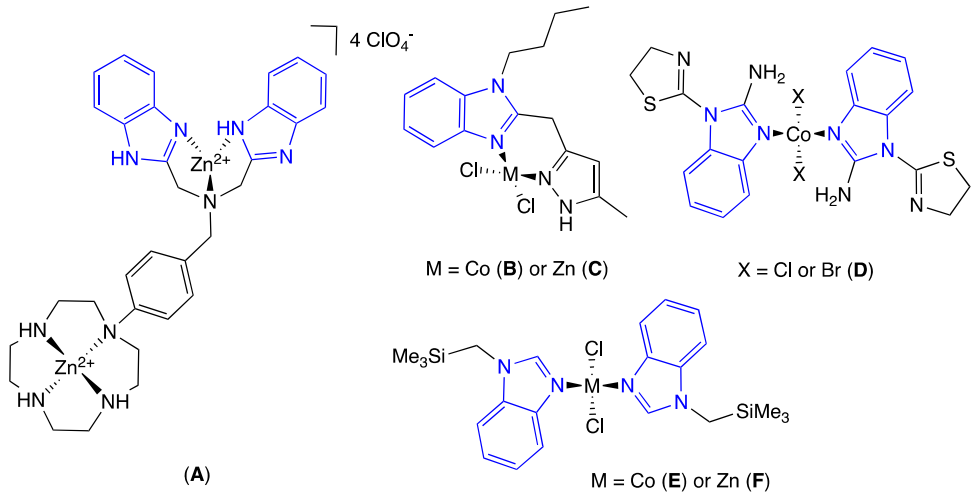


Fig. 2. Examples of reported cobalt(II) and zinc(II) complexes (**A-F**) studied as anticancer or antibacterial agents.

concentrations (MIC) as low as 0.0005 and 0.001 μmol/mL against *B. proteus* and *P. aeruginosa* strains, respectively. This dinuclear complex gave better antimicrobial efficiencies than the reference drug Chloromycin and the corresponding mono zinc(II) complex, in which the cation is not coordinated with the gangling benzimidazole moieties.[30] Starting from 1-butyl-2-((5-methyl-1H-pyrazol-3-yl)methyl)-1H-benzimidazole (**L**), the group of Garcia synthesized two *N*,*N*-chelate complexes of the type [MCl_2(**L**)] with M = Co (**B**) or Zn (**C**) (Fig. 2). The two complexes display good activities towards their antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* with MICs in the range 0.016 to 0.031 μmol/mL when complexes **B** and **C** were employed. Higher MICs (0.125 μmol/mL) were obtained for the tests carried out on the Gram-negative *Pseudomonas aeruginosa* microorganism.[31] Two cobalt(II) complexes in which the metal is coordinated to two 2-(2-aminobenzimidazole-1-yl)-2-thiazoline (**D**; Fig. 2) were evaluated by the group of Viñuelas-Zahínos for their antimicrobial activities on six gram-positive and gram-negative bacteria. The two tested cobalt(II) complexes led to high MICs (0.177 μmol/mL) for regardless of the bacteria used.[32] The cytotoxic properties of a cobalt(II) (**E**) and zinc(II) (**F**) (Fig. 2), in which the metal was coordinated to two 1-(trimethylsilyl) methyl-benzimidazole, were studied by the group of Küçükbay against the lung cancer A549 cell line. After 72 h of incubation, the cobalt(II) complex **E** was found to be 15 times more cytotoxic (IC_{50} = 3.98 μg/mL) than the zinc(II) complex **F**. Unfortunately, the selectivity of **E** towards healthy lung epithelial BEAS-2B cell line is low and its cytotoxic was the same as that observed with Cisplatin (IC_{50} = 2.94 μg/mL). Regarding antibacterial properties of complexes **E** and **F**, measured MIC values were very important, the lowest value (0.183 μmol/mL) was measured with complex **E** against *Staphylococcus aureus* strains.[33].

Based on the above considerations, we now report the synthesis of two series of *N*-alkylbenzimidazole-cobalt(II) and zinc(II) complexes, in which two benzimidazole entities were coordinated through their nitrogen atom to the metal, and evaluation of their antimicrobial activities against Gram-negative, Gram-positive and Fungi strains.

2. Experimental

The starting materials and reagents used in the reactions were purchased from Sigma-Aldrich Chemical Co or Merck Chemical Co and used without any purification. *N*-alkylbenzimidazole derivatives and complexes were prepared under inert atmosphere. Melting points were recorded in glass capillaries under air with an Electrothermal-9200 melting point apparatus melting points are reported as uncorrected values. FT-IR spectra were recorded with Perkin Elmer 100 spectrometer. Elemental analyses were done by İnönü University Scientific and Technology Center. ^{1}H NMR and ^{13}C{^{1}H} NMR were referenced to residual protonated solvents (δ = 7.26 ppm and 77.16 ppm for $CDCl_3$ with tetramethylsilane, respectively, and 2.50 ppm and 39.52 ppm for $(CD_3)_2SO$, respectively). 1-Allyl-benzimidazole (**1a**),[34] 1-methallyl-benzimidazole (**1b**),[34] 1-isopropyl-benzimidazole (**1c**),[35] 1-(3-methyloxetan-3-yl)methyl-benzimidazole (**1d**),[36] 1-allyl-5,6-dimethyl-benzimidazole (**1e**),[37] 1-methallyl-5,6-dimethyl-

benzimidazole (**1f**),[38] 1-isopropyl-5,6-dimethyl-benzimidazole (**1g**) [39] and 1-(3-methyloxetan-3-yl)methyl-5,6-dimethyl-benzimidazole (**1h**)[36] were prepared by literature procedures.

2.1. General procedure for the preparation of N-alkylbenzimidazole-cobalt(II) complexes (2a-h)

The azole-cobalt complexes were synthesized according to reported procedure.[34] In a Schlenk tube under an inert atmosphere of argon, a solution of $CoCl_2{\cdot}6H_2O$ (0.05 mmol) in methanol (5 mL) was added to a solution *N*-alkyl-substituted benzimidazole derivative **1a-h** (0.10 mmol) in chloroform (5 mL). The resulting mixture was stirred at room temperature. After for 4 h, diethylether (25 mL) was added to the solution, which caused precipitation of the cobalt(II) complex. The blue precipitate was filtered, washed with diethylether (3 × 10 mL) and dried under vacuum to give complexes **2a-h**. The paramagnetic behavior of cobalt (II) complexes allows the unique observation of broad singlet signals in ^{1}H NMR. Therefore, the spectra will be described in the range of 0 to 16 ppm without proton attribution and with relative intensities.

2.1.1. Dichloro-bis(1-allylbenzimidazole)cobalt(II) (2a)

Yield: 91 %; m.p.: 201–202 °C; FT-IR: $\nu_{(CN)}$ 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (1H), 3.04 (1H), 5.20 (1H), 6.50 (1H), 6.65 (1H), 9.25 (1H), 15.35 (2H) ppm. Elemental analysis (%): calcd for $C_{20}H_{20}Cl_2N_4Co$ (446.24): C: 53.83; H: 4.52; N: 12.56; found C: 53.86; H: 4.69; N: 12.71.

2.1.2. Dichloro-bis[1-(2-methallyl)benzimidazole]cobalt(II) (2b)

Yield: 88 %; m.p.: 224–225 °C; FT-IR: $\nu_{(CN)}$ 1518 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.94 (1H), 3.10 (2H), 5.22 (1H), 5.83 (1H), 6.11 (1H), 14.86 (1.5H) ppm. Elemental analysis (%): calcd for $C_{22}H_{24}Cl_2N_4Co{\bullet}1/2CH_3OH$ (490.32): C: 55.12; H: 5.34; N: 11.43. Found C: 54.99; H: 5.25; N: 11.78.

2.1.3. Dichloro-bis(1-isopropylbenzimidazole)-cobalt(II) (2c)

Yield: 88 %; m.p.: 207–208 °C; FT-IR: $\nu_{(CN)}$ 1507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (0.5H), 3.14 (1H), 5.26 (1H), 5.91 (6H) ppm. Elemental analysis (%): calcd for $C_{20}H_{24}Cl_2N_4Co{\bullet}1/2CH_3OH$ (466.30): C: 52.80; H: 5.62; N: 12.02. Found C: 52.69; H: 5.56; N: 12.33.

2.1.4. Dichloro-bis(1-((3- methyloxetan-3-yl)methyl)benzimidazole)-cobalt(II) (2d)

Yield: 86 %; m.p.: 145–146 °C; FT-IR: $\nu_{(CN)}$ 1511 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 1.16 (1H), 1.51 (5H), 4.32 (1H), 4.64 (1H), 6.26 (2H) ppm. Elemental analysis (%): calcd for $C_{24}H_{28}Cl_2N_4O_2Co$ (534.36): C: 53.95; H: 5.28; N: 10.49. Found C: 54.65; H: 5.82; N: 9.81.

2.1.5. Dichloro-bis(1-allyl-5,6-dimethylbenzimidazole)-cobalt(II) (2e)

Yield: 89 %; m.p.: 227–228 °C; FT-IR: $\nu_{(CN)}$ 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.29 (3H), 3.22 (3H), 6.43 (1H), 6.56 (1H), 9.25 (1H), 15.42 (2H) ppm. Elemental analysis (%): calcd for $C_{24}H_{28}Cl_2N_4Co$ (502.35): C: 57.38; H: 5.62; N: 11.15. Found C: 57.28; H: 5.53; N: 11.02.

2.1.6. Dichloro-bis(1-methallyl-5,6-dimethylbenzimidazole)-cobalt(II) (2f)

Yield: 91 %; m.p.: 230–231 °C, FT-IR: $\nu_{(CN)}$ 1511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.35 (3H), 3.17 (5H), 5.89 (1H), 6.13 (1H), 15.23 (2H) ppm. Elemental analysis (%): calcd for $C_{26}H_{32}Cl_2N_4Co{\bullet}2CH_3OH$ (594.49): C: 56.57; H: 6.78; N: 9.42. Found C: 56.02; H: 5.67; N: 9.71.

2.1.7. Dichloro-bis(1-isopropyl-5,6-dimethylbenzimidazole)-cobalt(II) (2g)

Yield: 88 %; m.p.: 201–202 °C; FT-IR: $\nu_{(CN)}$ 1503 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.35 (3H), 0.13 (3H), 3.46 (3H), 5.47 (7H) ppm. Elemental analysis (%): calcd for $C_{24}H_{32}Cl_2N_4Co{\bullet}CH_3OH$ (538.43): C: 55.77; H: 6.74; N: 10.41. Found C: 55.43; H: 6.02; N: 11.60.

2.1.8. Dichloro-bis(1-((3-methyloxetan-3-yl)methyl)-5,6-dimethylbenzimidazole)-cobalt(II) (2h)

Yield: 84 %, m.p.: 273–274 °C; FT-IR: $\nu_{(CN)}$ 1511 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 1.47 (2H), 2.34 (1H), 4.54 (1H), 5.01 (1H), 7.51 (1H) ppm. Elemental analysis (%): calcd for $C_{28}H_{36}Cl_2N_4O_2Co{\bullet}CH_3OH$ (622.50): C: 55.95; H: 6.48; N: 9.00. Found C: 55.98; H: 6.17; N: 9.17.

2.1.9. General procedure for the preparation N-alkylbenzimidazole-zinc(II) complexes (3a-h)

The azole-zinc complexes were synthesized according to reported procedure.[40] In a Schlenk tube under an inert atmosphere of argon, a solution of $ZnCl_2$ (0.05 mmol) and *N*-alkyl-substituted benzimidazole derivative **1a-h** (0.10 mmol) in ethanol (10 mL) was stirred at room temperature. After 4 h, the formed precipitate was filtered, washed with diethylether (3 × 10 mL) and dried under vacuum to give complexes **3a-h** as white solids.

2.1.10. Dichloro-bis(1-allylbenzimidazole)-zinc(II) (3a)

Yield 89 %; m.p.: 196–197 °C; FT-IR: $\nu_{(CN)}$ 1513 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 5.05 (d, 4H, NCH_2, $^3J_{HH}$ = 5.6 Hz), 5.17 (d, 2H, NCH_2CHCH_2, $^3J_{HH}$ = 17.2 Hz), 5.25 (d, 2H, NCH_2CHCH_2, $^3J_{HH}$ = 10.4 Hz), 6.00–6.01 (m, 2H, NCH_2CHCH_2), 7.30–7.38 (m, 4H, CH arom), 7.66 (d, 2H, arom CH, $^3J_{HH}$ = 7.6 Hz), 7.86 (d, 2H, arom CH, $^3J_{HH}$ = 8.0 Hz), 8.67 (s, 2H, NC*H*N); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$): δ = 47.26 (s, NCH_2), 118.45 (s, NCH_2CHCH_2), 132.83 (s, NCH_2CHCH_2), 111.80, 123.31, 123.78, 133.02, 140.05 (6 s, arom Cs), 144.85 (s, N*C*HN) ppm. Elemental analysis (%): calcd for $C_{20}H_{20}Cl_2N_4Zn$ (452.70): C: 53.07; H: 4.45; N: 12.38. Found C: 53.47; H: 4.40; N: 12.31.

2.1.11. Dichloro-bis(1-methallyl)benzimidazole)-zinc(II) (3b)

Yield: 88 %; m.p.: 179–180 °C; FT-IR: $\nu_{(CN)}$ 1519 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 6H, $NCH_2C(CH_3)CH_2$), 4.76 (s, 4H, NCH_2), 4.80 (s, 2H, $NCH_2C(CH_3)CH_2$), 4.99 (s, 2H, $NCH_2C(CH_3)CH_2$), 7.25–7.41 (m, 4H, CH arom), 8.01 (d, 2H, CH arom, $^3J_{HH}$ = 7.2 Hz), 8.59 (s, 2H, NC*H*N); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 19.87 (s, $NCH_2C(CH_3)CH_2$), 52.12 (s, NCH_2), 111.32 (s, $NCH_2C(CH_3)CH_2$), 138.35 (s, $NCH_2C(CH_3)CH_2$), 115.17, 118.95, 124.45, 124.75, 133.24, 139.59 (6 s, arom Cs), 144.72 (s, N*C*HN) ppm. Elemental analysis (%): calcd for $C_{22}H_{24}Cl_2N_4Zn$ (480.75): C: 54.96; H: 5.03; N: 11.65. Found C: 54.78; H: 4.99; N: 11.65.

2.1.12. Dichloro-bis(1-isopropylbenzimidazole)-zinc(II) (3c)

Yield: 86 %; m.p.: 201–202 °C; FT-IR: $\nu_{(CN)}$ 1506 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63 (d, 12H, $NCH(CH_3)_2$, $^3J_{HH}$ = 6.8 Hz), 4.71 (hept, 2H, $NCH(CH_3)_2$, $^3J_{HH}$ = 6.8 Hz), 7.27–7.36 (m, 4H, CH arom), 7.49 (d, 2H, CH arom, $^3J_{HH}$ = 8.0 Hz), 8.01 (d, 2H, CH arom, $^3J_{HH}$ = 8.0 Hz), 8.58 (s, 2H, NC*H*N); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 22.45 (s, NCH$(CH_3)_2$), 49.25 (s, $NCH(CH_3)_2$), 111.24, 119.12, 124.41, 124.48, 132.58, 139.91 (6 s, arom Cs), 141.70 (s, N*C*HN) ppm. Elemental analysis (%): calcd for $C_{20}H_{24}Cl_2N_4Zn$ (456.73): C: 52.60; H: 5.30; N: 12.27. Found C: 52.34; H: 5.25; N: 12.16.

2.1.13. Dichloro-bis[1-((3-methyloxetan-3-yl)methyl)benzimidazole]-zinc (II) (3d)

Yield: 82 %; m.p.: 153–154 °C; FT-IR: $\nu_{(CN)}$ 1513 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 1.22 (s, 6H, NCH_2CCH_3), 4.21 and 4.54 (AB spin system, 8H, CCH_2O, $^2J_{HH}$ = 4.8 Hz), 4.59 (s, 4H, NCH_2), 7.32–7.40 (m, 4H, CH arom), 7.80–7.86 (m, 4H, CH arom), 8.68 (s, 2H, NC*H*N); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$): δ = 21.85 (s, NCH_2CCH_3), 40.62 (s, NCH_2CCH_3), 50.22 (s, NCH_2CCH_3), 78.86 (s, CCH_2O), 111.77, 118.46, 123.14, 123.86, 134.00, 139.88 (6 s, arom Cs), 145.21 (s, N*C*HN) ppm. Elemental analysis (%): calcd for $C_{24}H_{28}Cl_2N_4O_2Zn{\cdot}2.5H_2O$ (585.85): C: 49.20; H: 5.68; N: 9.56. Found C: 49.06; H: 5.18; N: 9.15.

2.1.14. Dichloro-bis(1-allyl-5,6-dimethylbenzimidazole)-zinc(II) (3e)

Yield: 83 %; m.p.: 224–225 °C; FT-IR: $\nu_{(CN)}$ 1513 cm^{-1}; ^{1}H NMR (400

Table 1
Crystal data and structure refinement parameters for complexes **2c**, **2e** and **3b**.

Parameters	2c	2e	3b
CCDC depository	2,226,805	2,226,806	2,226,807
Color/shape	Blue/prism	Blue/prism	Colorless/prism
Chemical formula	$[CoCl_2(C_{10}H_{12}N_2)_2]$	$[CoCl_2(C_{12}H_{14}N_2)_2]$	$[ZnCl_2(C_{11}H_{12}N_2)_2]$
Formula weight	450.26	502.33	480.72
Temperature (K)	296(2)	296(2)	296(2)
Wavelength (Å)	0.71073 Mo Kα	0.71073 Mo Kα	0.71073 Mo Kα
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/n$ (No. 14)	P-1 (No. 2)	$P2_1/n$ (No. 14)
Unit cell parameters			
a, b, c (Å)	9.4799(6), 15.1378(10), 15.3230(11)	10.2108(19), 10.2572(17), 13.945(2)	10.8114(9), 14.5046(10), 15.2540(14)
α, β, γ (°)	90, 90.279(5), 90	108.078(13), 109.260(14), 92.290(14)	90, 94.554(7), 90
Volume (Å^3)	2198.9(3)	1294.2(4)	2384.5(3)
Z	4	2	4
$D_{calc.}$ (g/cm^3)	1.360	1.289	1.339
μ (mm^{-1})	1.035	0.887	1.269
Absorption correction	Integration	Integration	Integration
$T_{min.}$, $T_{max.}$	0.7518, 0.8562	0.6579, 0.9100	0.4636, 0.7750
F_{000}	932	522	992
Crystal size (mm^3)	0.49 × 0.31 × 0.28	0.79 × 0.26 × 0.11	0.79 × 0.26 × 0.17
Diffractometer/measurement method	STOE IPDS II/ω scan	STOE IPDS II/ω scan	STOE IPDS II/ω scan
Index ranges	$-12 \le h \le 11$, $-19 \le k \le 19$, $-19 \le l \le 19$	$-13 \le h \le 12$, $-13 \le k \le 12$, $-18 \le l \le 18$	$-13 \le h \le 13$, $-18 \le k \le 18$, $-19 \le l \le 19$
θ range for data collection (°)	$2.521 \le \theta \le 27.240$	$2.115 \le \theta \le 28.092$	$1.940 \le \theta \le 27.785$
Reflections collected	33,568	15,143	19,566
Independent/observed reflections	4861/3188	6045/3415	5386/3211
$R_{int.}$	0.1145	0.0723	0.1154
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	4861/0/248	6045/0/284	5386/21/274
Goodness-of-fit on F^2	1.168	0.913	1.004
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0705$, $wR_2 = 0.1071$	$R_1 = 0.0444$, $wR_2 = 0.0846$	$R_1 = 0.0532$, $wR_2 = 0.0999$
R indices (all data)	$R_1 = 0.1198$, $wR_2 = 0.1196$	$R_1 = 0.0988$, $wR_2 = 0.0986$	$R_1 = 0.1021$, $wR_2 = 0.1168$
$\Delta\rho_{max.}$, $\Delta\rho_{min.}$ (e/Å^3)	0.364, −0.232	0.347, −0.226	0.449, −0.537

MHz, $CDCl_3$): δ = 2.27 (s, 6H, $C_6H_2(CH_3)_2$), 2.33 (s, 6H, $C_6H_2(CH_3)_2$), 4.77 (d, 4H, NCH_2, $^3J_{HH}$ = 4.0 Hz), 5.20 (d, 2H, NCH_2CHCH_2, $^3J_{HH}$ = 17.2 Hz), 5.31 (d, 2H, NCH_2CHCH_2, $^3J_{HH}$ = 10.0 Hz), 5.91–6.01 (m, 2H, NCH_2CHCH_2), 7.15 (s, 2H, CH arom), 7.76 (s, 2H, arom CH), 8.42 (s, 2H, NCHN); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 20.40 (s, $C_6H_2(CH_3)_2$), 20.70 (s, $C_6H_2(CH_3)_2$), 48.36 (s, NCH_2), 118.92 (s, NCH_2CHCH_2), 133.73 (s, NCH_2CHCH_2), 110.94, 119.86, 130.90, 131.74, 134.26, 138.35 (6 s, arom Cs), 143.32 (s, NCHN) ppm. Elemental analysis (%): calcd for $C_{24}H_{28}Cl_2N_4Zn$ (508.81): C: 56.66; H: 5.55; N: 11.01. Found C: 56.50; H: 5.71; N: 11.02.

2.1.15. Dichloro-bis(1-methallyl-5,6-dimethylbenzimidazole)-zinc(II) (3f)

Yield: 81 %; m.p.: 215–216 °C; FT-IR: $\nu_{(CN)}$ 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 6H, $NCH_2C(CH_3)CH_2$), 2.24 (s, 6H, $C_6H_2(CH_3)_2$), 2.31 (s, 6H, $C_6H_2(CH_3)_2$), 4.69 (s, 4H, NCH_2), 4.76 (s, 2H, $NCH_2C(CH_3)CH_2$), 4.98 (s, 2H, $NCH_2C(CH_3)CH_2$), 7.12 (s, 2H, CH arom), 7.70 (s, 2H, CH arom), 8.40 (s, 2H, NCHN); $^{13}C\{^1H\}$ NMR (100 MHz, $(CD_3)_2SO$): δ = 19.89 (s, $NCH_2C(CH_3)CH_2$), 20.40 (s, $C_6H_2(CH_3)_2$), 20.72 (s, $C_6H_2(CH_3)_2$), 51.92 (s, NCH_2), 114.77 (s, $NCH_2C(CH_3)CH_2$), 138.60 (s, $NCH_2C(CH_3)CH_2$), 111.09, 118.68, 131.84, 133.74, 134.32, 138.20 (6 s, arom Cs), 143.61 (s, NCHN) ppm. Elemental analysis (%): calcd for $C_{26}H_{32}Cl_2N_4Zn{\cdot}0.5H_2O$ (545.86): C: 57.21; H: 6.09; N: 10.26. Found C: 57.09; H: 5.72; N: 10.56.

2.1.16. Dichloro-bis(1-isopropyl-5,6-dimethylbenzimidazole)-zinc(II) (3g)

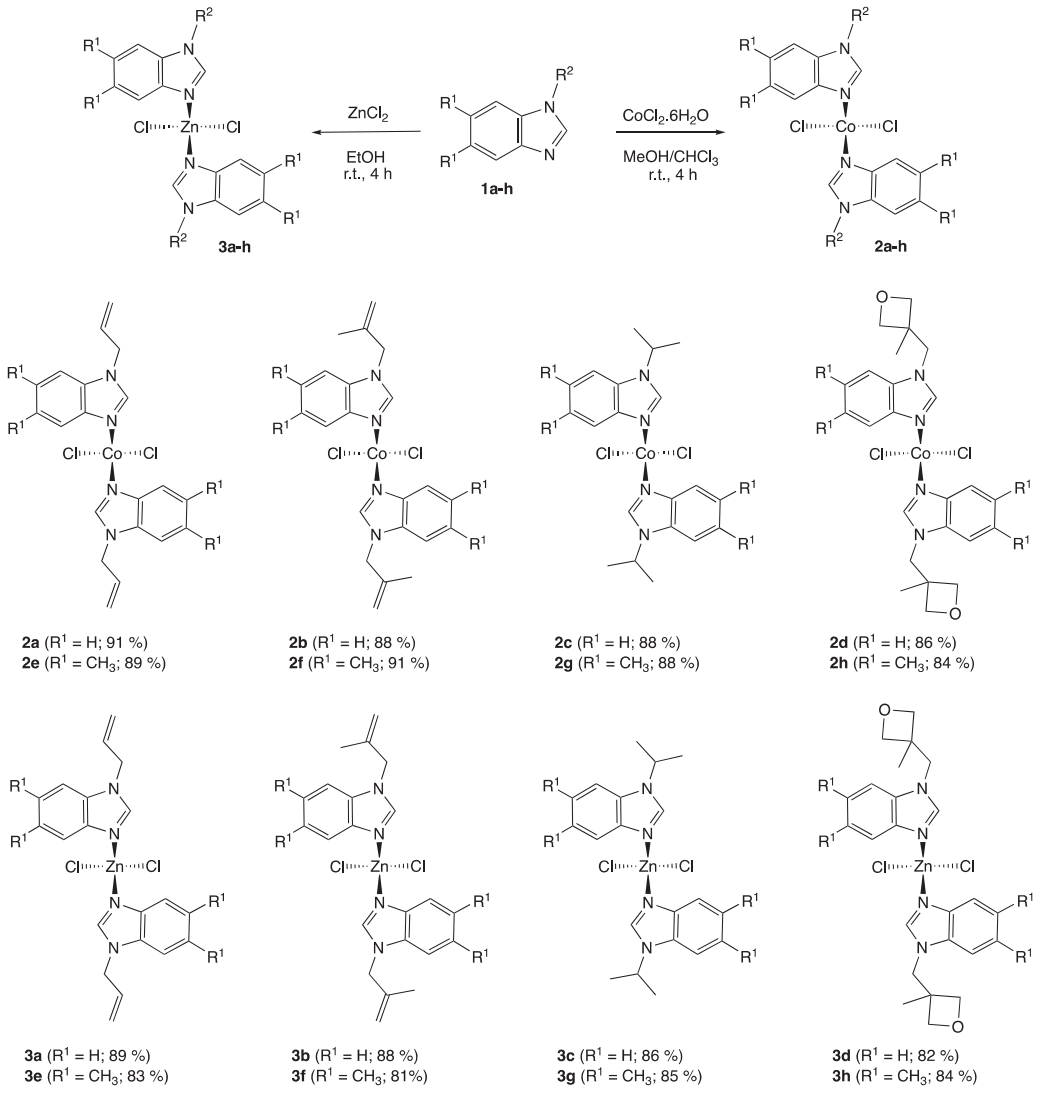
Yield: 85 %; m.p.: 249–250 °C; FT-IR: $\nu_{(CN)}$ 1503 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (d, 12H, $NCH(CH_3)_2$, $^3J_{HH}$ = 6.8 Hz), 2.27 (s, 6H, $C_6H_2(CH_3)_2$), 2.35 (s, 6H, $C_6H_2(CH_3)_2$), 4.64 (hept, 2H, $NCH(CH_3)_2$, $^3J_{HH}$ = 6.8 Hz), 7.23 (s, 2H, CH arom), 7.75 (s, 2H, CH arom), 8.44 (s, 2H, NCHN); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 20.40 (s, $C_6H_2(CH_3)_2$), 20.77 (s, $C_6H_2(CH_3)_2$), 22.49 (s, $NCH(CH_3)_2$), 49.04 (s, $NCH(CH_3)_2$), 111.12, 118.99, 131.20, 133.61, 133.94, 138.59 (6 s, arom Cs), 140.74 (s, NCHN) ppm. Elemental analysis (%): calcd for $C_{24}H_{32}Cl_2N_4Zn$ (512.84): C: 56.21; H: 6.29; N: 10.93. Found C: 55.87; H: 6.22; N: 10.95.

2.1.17. Dichloro-bis(1-((3-methyloxetan-3-yl)methyl)-5,6-dimethylbenzimidazole)-zinc(II) (3h)

Yield: 84 %; m.p.: 280–281 °C; FT-IR: $\nu_{(CN)}$ 1513 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 1.21 (s, 6H, NCH_2CCH_3), 2.28 (s, 6H, $C_6H_2(CH_3)_2$), 2.33 (s, 6H, $C_6H_2(CH_3)_2$), 4.20 and 4.53 (AB spin system, 8H, CCH_2O, $^2J_{HH}$ = 6.0 Hz), 4.50 (s, 2H, NCH_2), 7.55 (s, 2H, CH arom), 7.55 (s, 2H, CH arom), 8.46 (s, 2H, NCHN); $^{13}C\{^1H\}$ NMR (100 MHz, $(CD_3)_2SO$): δ = 19.92 (s, $C_6H_2(CH_3)_2$), 20.17 (s, $C_6H_2(CH_3)_2$), 21.85 (s, NCH_2CCH_3), 40.60 (s, NCH_2CCH_3), 50.10 (s, NCH_2CCH_3), 78.90 (s, CCH_2O), 111.37, 118.35, 131.51, 132.64, 138.88 (5 s, arom Cs), 144.09 (s, NCHN) ppm. Elemental analysis (%): calcd for $C_{28}H_{36}Cl_2N_4O_2Zn{\cdot}0.5H_2O$ (605.92): C: 55.50; H: 6.15; N: 9.25. Found C: 55.53; H: 6.05; N: 8.99.

2.2. X-ray crystallography

Single crystal X-ray data were collected on a STOE IPDS II diffractometer at room temperature using graphite-monochromated Mo Kα radiation by applying the ω-scan method. Data collection and cell refinement were carried out using X-AREA[41] whilst data reduction was applied using X-RED32.[41] The structures were solved by a dual-space algorithm using SHELXT-2014[42] and refined by means of the full-matrix least-squares calculations on F^2 using SHELXL-2018.[43] All H atoms were located in difference maps and then treated as riding atoms, fixing the bond lengths at 0.93, 0.98, 0.97 and 0.96 Å for aromatic CH and terminal CH_2, methine CH, methylene CH_2 and methyl CH_3 atoms, respectively. The carbon atom C22 in **3b** was disordered over two positions and the refined site-occupancy factors of the disordered atom are 0.654(8) for the major position and 0.346(8) for the minor position, respectively. The displacement parameters of the H atoms were fixed at $U_{iso}(H) = 1.2U_{eq}$ ($1.5U_{eq}$ for CH_3). Crystal data, data collection and structure refinement details are given in Table 1. Molecular graphics were generated by using OLEX2.[44].



Scheme 1. Synthesis of the bis-*N*-alkylbenzimidazole cobalt(II) **2a-h** and zinc(II) **3a-h** complexes.

2.3. Antimicrobial activity

The antimicrobial activity assays of *N*-alkylbenzimidazole-metal complexes **2a-h** and **3a-h** were tested using the modified agar dilution method recommended by the Clinical and Laboratory Standards Institute (CLSI).[45,46].

Minimal inhibitory concentrations (MIC) for each complex were determined as the lowest concentration preventing bacteria and fungi growth (American Type Culture Collection ATCC Rockville, MD, USA). Bacterial strains (*Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* MRSA ATCC 43300, *Klebsiella pneumoniae* ATCC 700603 and *Acinetobacter baumannii* ATCC 19606) were grown in Muller Hinton Broth (Merck) medium. Fungal strains (*Candida glabrata* ATCC 90030 and *Candida albicans* ATCC 14053) were grown in RPMI 1640 Broth (Sigma-Aldrich Chemie GmbH Taufkirchen, Germany) medium. The turbidity of bacteria and fungi matched that of a McFarland no. 0.5 turbidity standard.[47] The prepared bacterial and fungal standard inoculums were inoculated into the media as two series for control and growth was detected in all of them. Solutions of all compounds were prepared in DMSO. All dilutions were made with distilled water. Concentrations of test compounds are 800, 400, 200, 100, 50, 25, 12.5 and 6.25 μg/mL.

Ampicillin, Ciprofloxacin, Amikacin, Tigecycline, and Vancomycin were used as antibacterial standard drugs, while Fluconazole was used as an antifungal standard drug. Standard inoculum of bacteria and fungi (106 CFUs/mL) were inoculated with a sterile plastic ring-tipped loop (0.01 mL) on agar plates containing 800, 400, 200, 100, 50, 25, 12.5 and 6.25 μg/mL material. All planted plates were evaluated after they were kept in an oven at 35 °C for 16–20 h for bacteria and 48 h for fungi.

3. Result and discussion

3.1. Synthesis and characterization of bis-N-alkylbenzimidazole cobalt (II) and zinc(II) complexes

Having in hands four 1-alkyl-benzimidazoles (**1a-d**) and four 1-alkyl-5,6-dimethyl-benzimidazoles (**1e-h**), in which the alkyl substituent is either an allyl, methallyl, isopropyl or 3-methyloxetan-3-yl)methyl chain, two series of cobalt(II) (**2a-h**) and zinc(II) (**3a-h**) complexes of the type $[MCl_2(\mathbf{1})_2]$ (M = Co or Zn) were prepared. The complexes were obtained by reaction between the either $CoCl_2{\cdot}6H_2O$ or $ZnCl_2$ metal sources and two equivalents of ligand **1a-h**. After stirring at room temperature during 4 h, the complexes were isolated as blue or white solids for the cobalt(II) **2a-h** (yields 84–91 %) and the zinc(II) **3a-h** complexes (yields 81–89 %), respectively (Scheme 1). The latter complexes, which were stable to air and moisture in solid and solution, were characterized by elemental analysis, FT-IR and multinuclear NMR

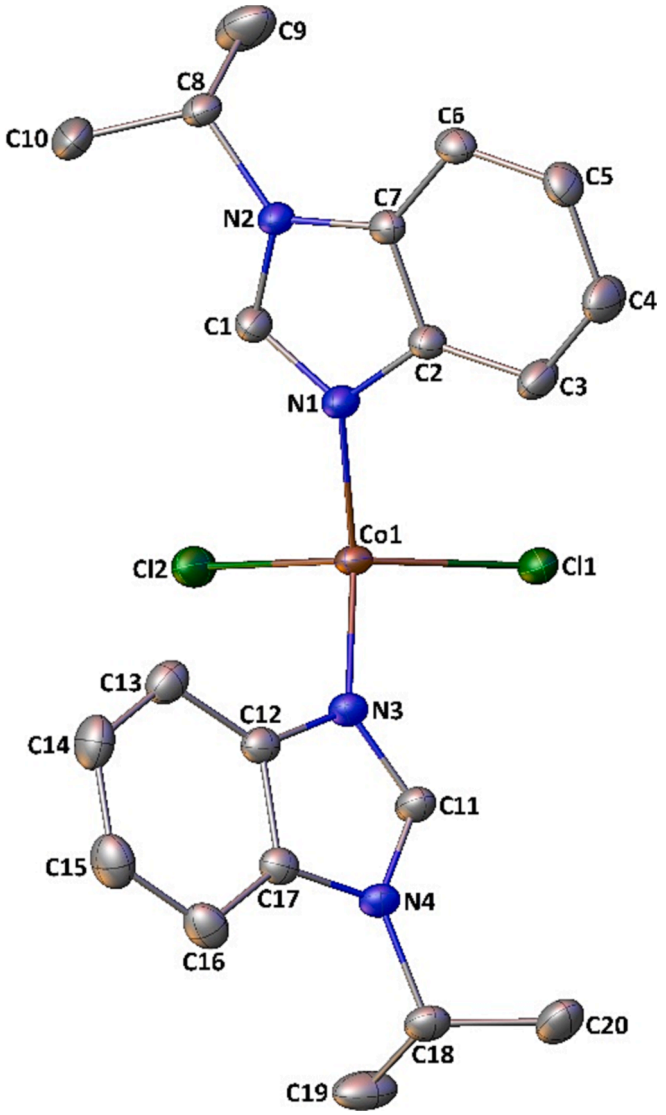


Fig. 3. Molecular structure of 3**c**. The OLEX2 drawing, with 20% probability thermal ellipsoid, shows the atom-labeling. For clarity, H atoms have been omitted.

spectroscopy (^{1}H and ^{13}C) (see the experimental section and Supplementary Materials). The formation of [MCl_2(**1**)$_2$] (M = Co or Zn) complexes was unambiguously deduced from the elemental analysis, which perfectly fitted with the presence of two 1-alkyl-benzimidazole moieties.

The blue cobalt(II) complexes **2a-h** have paramagnetic properties due to 3d configuration of cobalt(II) cation, only few signals could be observed in the range 0 to 16 ppm in their ^{1}H NMR spectra,[48,49] therefore these complexes were characterized by elemental analysis and FT-IR. The FT-IR spectra of *N*-alkylbenzimidazole derivatives **1a-h** displayed a characteristic band in the range 1471–1494 cm^{-1} assigned to C=N vibrations, after coordination to the cobalt(II) cation, these bands shift towards higher values (1503–1519 cm^{-1}).

The white zinc(II) complexes **3a-h** also displayed in their FT-IR spectra the specific C=N vibration of the ligand in the range 1503–1519 cm^{-1}. Their NMR analysis revealed, for each complex, the expected signal in the range 8.40–8.68 and 140.74–145.21 ppm in their ^{1}H and ^{13}C NMR spectra, respectively, attributed to the NCHN signals. [50].

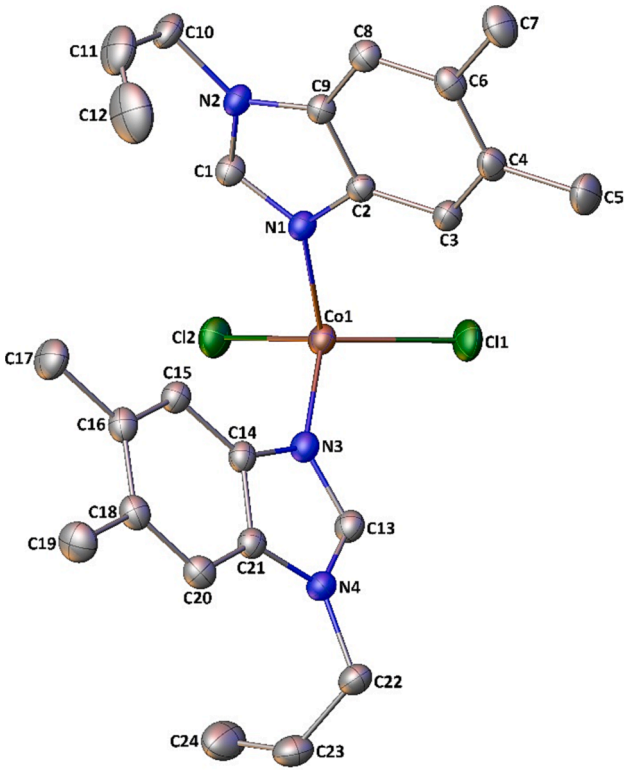


Fig. 4. Molecular structure of **2e**. The OLEX2 drawing, with 20% probability thermal ellipsoid, shows the atom-labeling. For clarity, H atoms have been omitted.

3.2. X-ray crystallographic analysis

The formation of the cobalt(II) and zinc(II) complexes coordinated to two benzimidazole moieties was confirmed by single X-ray diffraction studies. Single crystals of complexes **2c, 2e** and **3b** (Figs. 3-5) were obtained by slow diffusion of diethylether into a dichloromethane solution of the complex.

The complexes **2c** and **3b** crystallize in the monoclinic form with the $P2_1/n$ space group while complex **2e** crystallizes in the triclinic form with the *P*-1 space group. The cobalt(II) and zinc(II) cations adopt a pseudo-tetrahedral geometry with two benzimidazole ligands and chlorine atoms occupying four sites of the tetrahedron. The bond lengths of Co-Cl and Co-N were found to be 2.2691(12), 2.2464(12), 2.028(3) and 2.023(3) Å, respectively in complex **2c** and 2.2513(8), 2.2432(9), 2.040(2) and 2.009(2) Å, respectively, in complex **2e**. Note that, the bond lengths (2.2440(6), 2.2274(6), 2.0041(15) and 2.0147(15) Å, respectively) are close to those reported in the dichloro-bis(1-allylbenzimidazole)cobalt(II) complex.[34] For the complex **3b**, the bond lengths of Zn-Cl and Zn-N, 2.2264(9), 2.2583(10), 2.036(3) and 2.024(3) Å, respectively, are similar to those found in the related dichloro-bis(1-methylbenzimidazole)-zinc(II), 2.235(6), 2.2415(6), 2.0234(16) and 2.0258(16) Å, respectively.[51] The dihedral angle between the two benzimidazole ring planes is 71.93° in **2c**, 89.03° in **2e** and 79.80° in **3b** while the internal N-CH-N ring angle ranges from 112.7(4) to 113.6(2)° (Table 2).

In the solid state, the complexes **2c, 2e** and **3b** selft organized in infinite chains, in which the complexes were supramolecularly linked via CH•••Cl (2.755 Å in complex **2c** or 2.780 and 2.815 Å in complex **3c**) or π-π (distance between the centroid of C_6H_4 and C_3N_2H aromatic rings of benzimidazole is 3.977 Å in complex **2e**) interactions (see Supplementary Materials).

The geometry of each metal ion is best described as a distorted tetrahedral configuration which is evident from the angles changing

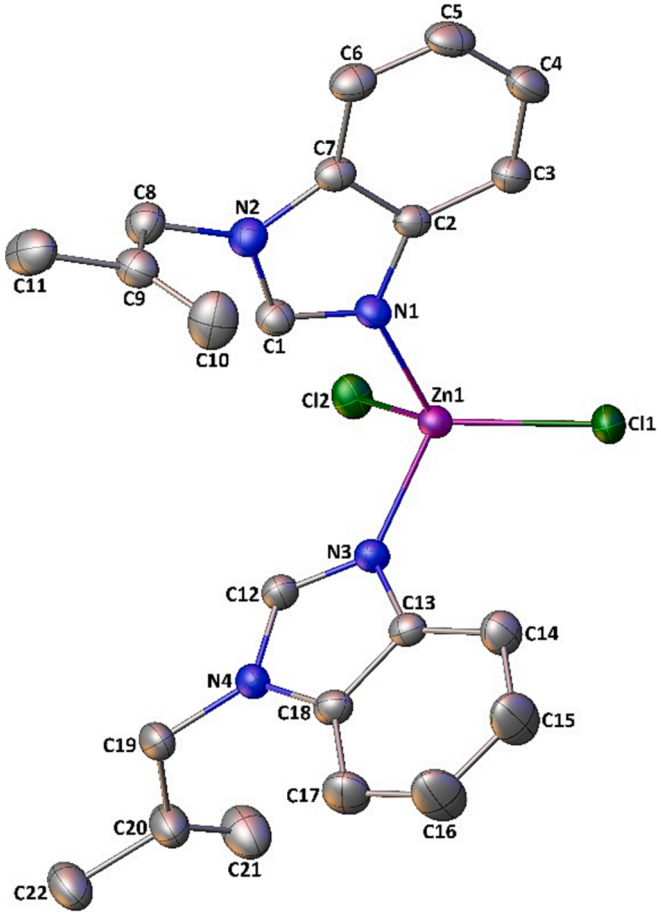


Fig. 5. Molecular structure of **3b**. The OLEX2 drawing, with 20% probability thermal ellipsoid, shows the atom-labeling. For clarity, H atoms have been omitted and only the main position for the disorder C22 atom was represented (0.654(8)).

Table 2
Selected geometric parameters for complexes **2c**, **2e** and **3b**.

Parameters	2c	2e	3b
Bond lengths (Å)			
M−Cl1	2.2691(12)	2.2513(8)	2.2264(9)
M−Cl2	2.2464(12)	2.2432(9)	2.2583(10)
M−N1	2.028(3)	2.040(2)	2.036(3)
M−N3	2.023(3)	2.009(2)	2.024(3)
N1-C1	1.322(5)	1.334(3)	1.333(5)
N2-C1	1.346(5)	1.348(4)	1.344(5)
N3-C11/C13/C12	1.326(5)	1.342(3)	1.329(5)
N4-C11/C13/C12	1.340(5)	1.332(4)	1.337(5)
Angles (°)			
Cl1-M−Cl2	120.07(5)	116.43(4)	117.77(5)
Cl1-M−N1	106.12(9)	108.33(7)	113.98(9)
Cl1-M−N3	102.73(9)	107.69(7)	112.88(8)
Cl2-M−N1	104.74(9)	106.58(6)	104.15(8)
Cl2-M−N3	106.22(9)	110.50(7)	103.28(9)
N1-M−N3	117.78(14)	106.91(9)	103.17(12)
N1-C1-N2	113.3(3)	113.6(2)	112.7(4)
N3-C11/C13/C12-N4	113.5(4)	113.5(3)	113.9(3)
Geometry indexes			
$\tau_4/\tau_4^{'}$	0.87/0.86	0.94/0.93	0.91/0.90

Note: *M* is the metal atom, Co in **2c** and **2e** and Zn in **3b**.

from 102.73(9) to 120.07(5)° in **2c**, from 106.58(6) to 116.43(4)° in **2e** and from 103.17(12)° to 117.77(5)° in **3b**. For quantitative evaluation of the extent of distortion around the metal centers, the structural indexes τ_4 [52] and $\tau_4^{'}$ [53] were employed;

$$\tau_4 = \frac{360^{\circ} - (\alpha + \beta)}{360^{\circ} - 2\theta} \qquad \tau_4^{'} = \frac{\beta - \alpha}{360^{\circ} - \theta} + \frac{180^{\circ} - \beta}{180^{\circ} - \theta}$$

where α and β ($\beta > \alpha$) are the two greatest valence angles and θ is the ideal tetrahedral angle (109.5°). The τ_4 and $\tau_4^{'}$ values for ideal square-planar and perfect tetrahedral coordination spheres are 0 and 1, respectively. The calculated τ_4 and $\tau_4^{'}$ geometry indices are 0.87 and 0.86 for **2c**, 0.94 and 0.93 for **2e** and 0.91 and 0.90 in **3b**, respectively, indicating a distorted tetrahedral geometry.

3.3. Antimicrobial activities of bis-N-alkylbenzimidazole Co(II) and Zn (II) complexes

The antibacterial activities of cobalt(II) **2a-h** and zinc(II) **3a-h** complexes were evaluated against Gram-negative (*Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia,* and *Acinetobacter baumannii*), Gram-positive (*Staphylococcus aureus, Staphylococcus aureus MRSA,* and *Enterococcus faelacis*) and fungal (*Candida albicans* and *Candida glabrata*) strains at different concentrations and ranking with standard drugs (Ampicillin, Amikacin, Ciprofloxacin, Fluconazole, Vancomycin and Tigecycline). The antimicrobial activities of organometallic drugs were determined in terms of their minimal inhibitory concentrations (MIC) values, which were defined as the lowest concentration of the antimicrobial that visibly inhibits the growth of microbes after incubation overnight. The MIC values of synthesized compounds are summarized in Table 3.

As interfered from Table 3, all tested complexes inhibited the growth of all bacterial and fungal strains with MIC values between 0.024 and 1.592 μmol/mL. Interestingly, they displayed higher inhibition activity against fungi than against Gram-positive and Gram-negative bacteria strains. When we compared the nature of the metal, cobalt(II) or zinc(II), coordinated to the same *N*-alkylbenzimidazole ligand, we can observe that cobalt(II) complexes (**2a-h**) were more poison against microorganisms than zinc(II) complexes (**3a-h**), as example, when *Klebsiella pneumoniae* was treated with complexes generated from 1-(3-methyl-oxetan-3-yl)methyl-benzimidazole (**1d**), MIC values of 0.092 and 0.740 μmol/mL were measured with the cobalt(II) complex **2d** and the zinc(II) complex **3d**, respectively. Among cobalt(II) complexes **2a-h**, the **2f** complex, bearing 1-methallyl-5,6-dimethyl-benzimidazole as ligands, displayed the higher antibacterial activities against Gram-negative and Gram-positive strains of MIC values between 0.047 and 0.188 μmol/mL.

Regarding the antifungal properties of these complexes, the cobalt-based derivatives were more effective (MIC values in the range 0.024–0.092 μmol/mL) than their zinc-based counterparts (MIC values in the range 0.049–0.370 μmol/mL). It is interesting to note that, here too, the nature of the 1-alkylbenzimidazole ligand plays a determining role in the effectiveness of cobalt(II) complexes. As before, the nature of the alkyl chains modulates the antifungal activities, we can also observe that the presence of methyl substituents on the benzimidazole cycle is essential. In fact, when 5,6-dimethyl-benzimidazole (complexes **2e** and **2f**) was employed as skeleton instead of benzimidazole (complexes **2a** and **2b**), MIC values as low as 0.024 μmol/mL were measured, the latter values were close to those obtained when the related dichloro-bis-(1-(4-chlorobenzyl)-5-methylbenzimidazole)cobalt(II) complex[55] and the commercially available drug Fluconazole were employed (0.020 μmol/mL).

4. Conclusion

In the present article, we described the synthesis of sixteen novel complexes of the type $[MCl_2L_2]$, in which the metal was either cobalt(II) or zinc(II) and the ligand (**L**) was an *N*-alkyl-benzimidazole or an *N*-alkyl-5,6-dimethyl-benzimidazole. These complexes were isolated in high yields and fully characterized by FT-IR, elemental analysis, ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy for the diamagnetic complexes. The

Table 3
Minimal inhibitory concentrations (μmol/mL).

Compound	Gram-negative				Gram-positive			Fungi	
	Escherichia coli	*Pseudomonas aeruginosas*	*Acinetobacter baumannii*	*Klebsiella pneumoniae*	*Staphylococcus aureus*	*Staphlococcus aureus MRSA*	*Enterococcus faecalis*	*Candida albicans*	*Candida glabrata*
2a	0.112	0.896	0.896	0.112	0.112	0.112	0.112	0.056	0.056
2b	0.105	0.422	0.422	0.105	0.105	0.105	0.105	0.053	0.053
2c	0.222	0.888	0.888	0.222	0.222	0.222	0.222	0.056	0.056
2d	0.092	0.749	0.749	0.092	0.187	0.187	0.187	0.092	0.092
2e	0.199	1.592	1.592	0.199	0.199	0.199	0.398	0.025	0.025
2f	0.094	0.188	0.188	0.094	0.047	0.047	0.047	0.024	0.024
2 g	0.197	0.395	0.395	0.197	0.197	0.197	0.197	0.049	0.049
2 h	0.085	0.339	0.339	0.085	0.339	0.339	0.339	0.085	0.085
3a	0.442	0.884	0.884	0.442	0.442	0.442	0.884	0.055	0.110
3b	0.208	0.832	0.832	0.208	0.416	0.416	0.416	0.052	0.052
3c	0.219	0.876	0.876	0.219	0.219	0.219	0.219	0.109	0.109
3d	0.740	1.479	1.479	0.740	0.740	0.740	0.740	0.370	0.370
3e	0.393	0.786	0.786	0.393	0.196	0.196	0.196	0.049	0.049
3f	0.186	0.372	0.372	0.186	0.186	0.186	0.372	0.093	0.093
3 g	0.390	0.780	0.780	0.390	0.195	0.195	0.390	0.049	0.097
3 h	0.670	1.340	1.340	0.670	0.670	0.670	0.670	0.335	0.335
Ampicillin	0.009	/	/	0.004	0.004	/	0.004	/	/
Amikacin	/	0.003	0.005	0.003	/	/	/	/	/
Ciprofloxacin	0.005	/	/	0.005	/	/	/	/	/
Fluconazole	/	/	/	/	/	/	/	0.020	0.010
Vancomycin	/	/	/	/	/	0.002	/	/	/
Tigecycline	/	/	0.003	/	/	/	/	/	/

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

tetrahedral geometry of the complexes was unambiguously confirmed by three single-crystal X-ray structures.

The antimicrobial properties of the sixteen complexes were evaluated against a series of Gram-negative, Gram-positive and fungi strains (*Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Staphylococcus aureus, methicillin-resistant S. aureus*, *Enterococcus faecalis*, *Candida albicans* and C*andida glabrata*). Antibacterial tests revealed that cobalt(II) complexes were more effective than their related zinc(II) complexes with MIC values as low as 0.047 μmol/mL when the dichloro-*bis*(1-methallyl-5,6-dimethylbenzimidazole)-cobalt(II) complex was employed against Gram-positive bacteria. The latter complex displayed a fungicidal activity even higher with MIC values of 0.024 μmol/mL, close to those obtained with the commercially available drug Flucanozole, against *Candida albicans* and *Candida glabrata* fungi.

The antibacterial and antifungal studies have highlighted the importance of the choice of the metal as well as the substitutes on the benzimidazole skeleton, optimization of these complexes will be the subject of future studies.

CRediT authorship contribution statement

Neslihan Şahin: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Elvan Üstün:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision. **İlknur Özdemir:** Conceptualization, Supervision. **Selami Günal:** Methodology, Validation, Investigation. **Namık Özdemir:** Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft. **Hakan Bülbül:** Methodology, Software, Validation, Formal analysis, Investigation. **Nevin Gürbüz:** Conceptualization, Supervision. **İsmail Özdemir:** Conceptualization, Supervision. **David Sémeril:** Conceptualization, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgement

This work is supported by the Scientific Research Project Fund of Sivas Cumhuriyet University under the project number F-461.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inoche.2023.111396.

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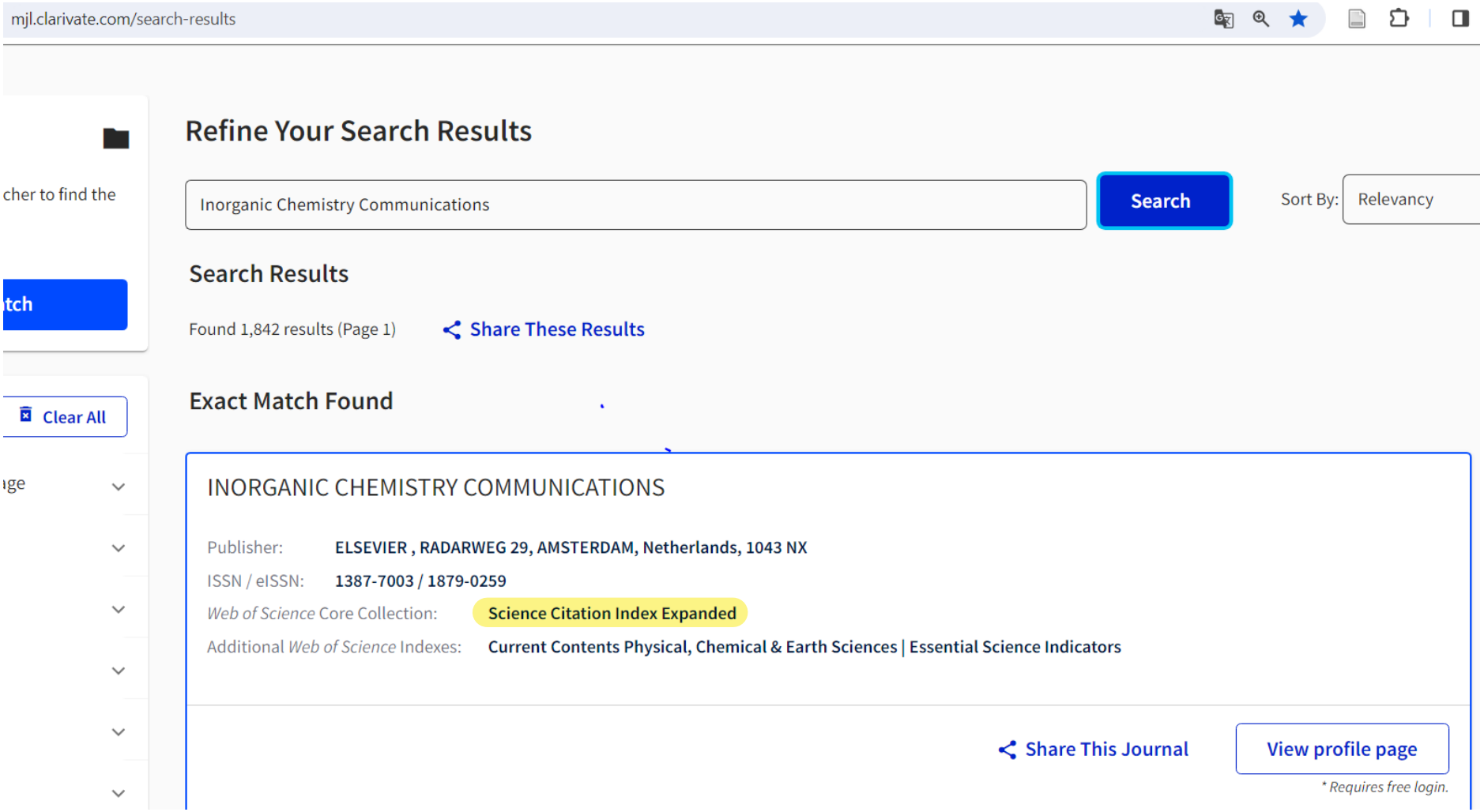
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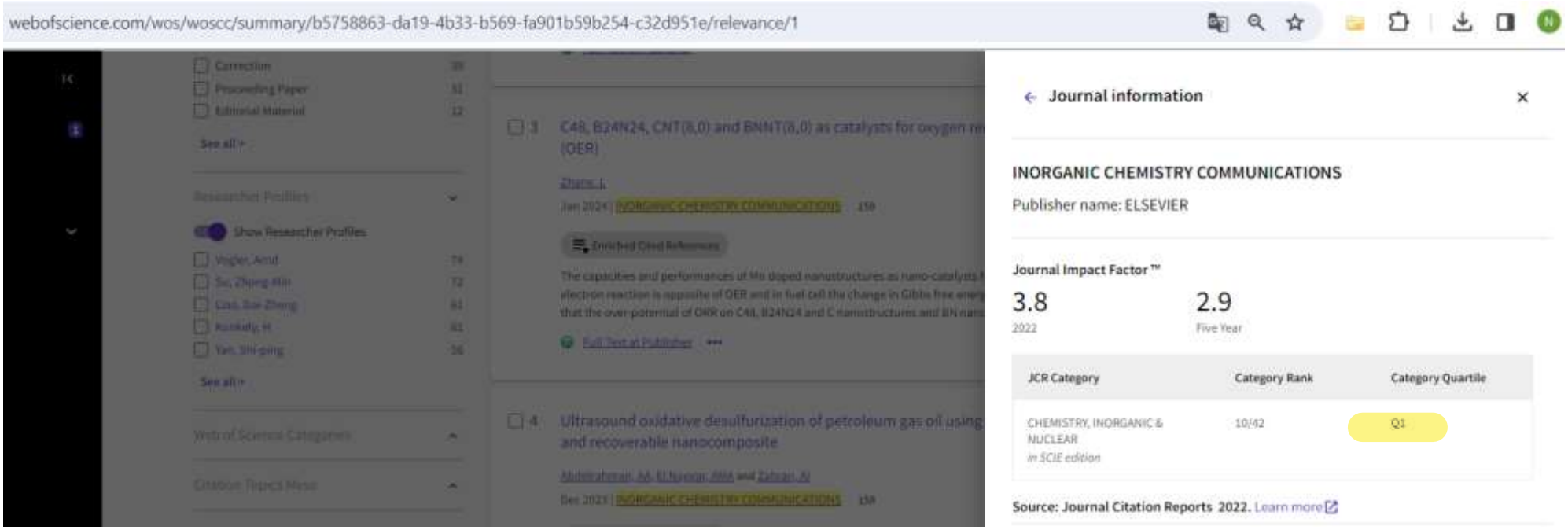
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